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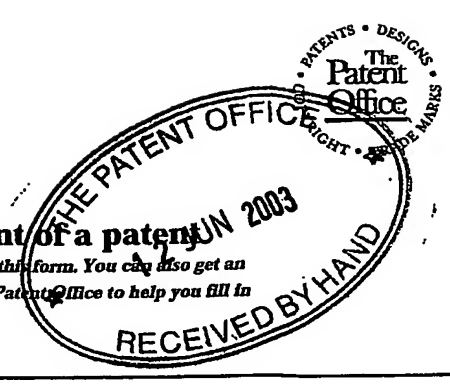

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1. Your reference — HP/LP6153621 — 12 JUN 2003

2. Patent application number *(The Patent Office will fill in this part)* — 0313630.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

THE WWK TRUST
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Beckenham
Kent
BR3 1BN

Patents ADP number *(if you know it)* 8029852001

If the applicant is a corporate body, give the country/state of its incorporation — GB

4. Title of the invention — COMPOSITIONS FOR THE ENHANCED TREATMENT OF DEPRESSION

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

MEWBURN ELLIS
York House
23 Kingsway
London WC2B 6HP

Patents ADP number *(if you know it)* — 109006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
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YES

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Description	11
Claim *(s)*	6
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	1
Request for preliminary examination and search *(Patents Form 9/77)*	0
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Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this application.

Signature Hugh Paget Date 12 JUNE 2003

12. Name and daytime telephone number of person to contact in the United Kingdom HUGH C. E. PAGET - 020 7240 4405

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DUPLICATE

COMPOSITIONS FOR THE ENHANCED TREATMENT OF DEPRESSION

TECHNICAL FIELD

The present invention relates to the use of a combined medicament in the enhanced treatment of various forms of depression. The invention also relates to the preparation of medicaments for such treatments.

BACKGROUND OF THE INVENTION AND PRIOR ART

Depression is a psychiatric condition resulting from a disorder of mood. Depression has been recognised as a major disease for centuries. In addition to disorder of mood, patients are at risk of self harm, or even suicide attempts, either successful or unsuccessful.

Depression is thought to result from failure of normal neurotransmitter function where there is failure to produce sufficient neurotransmitter. This often arises as a result of neurotransmitter imbalance. Depression may in part arise from altered efficiency of receptor signalling or from a relative deficiency of neurotransmitter.

Detectable depression occurs in approximately 10% of the general population. Some 20% of depressive patients show moderate to severe symptoms, the severity of which is generally thought to be linked to the duration of depression and the level of control using antidepressants.

Depression may be mild, for example taking the form of a mild mood change. Moderate to severe symptoms of depression can result in self harm or even progress to psychosis.

Previous treatments for depression have included tricyclic antidepressants on their own, monamine oxidase inhibitors (MAOI) and selective serotonin re-uptake inhibitors (SSRI). The amino acid L-tryptophan is also effective, but none of the other amino acids have previously shown clinical benefit, either in combination or on their own.

WO 96/11009 discloses treatment of multiple sclerosis and WO 98/01157 discloses the treatment of peripheral neuropathies by some of the combinations of components employed in the present invention.

Vitamin B_{12} has been proposed for the treatment of B_{12}-deficiency associated neuropathy.

DISCLOSURE OF THE INVENTION

The present inventor has surprisingly found that a combination of a tricyclic antidepressant, a monamine oxidase inhibitor (MAOI) or a selective serotonin re-uptake inhibitor (SSRI) with an inducer or a precursor of a neurotransmitter can enhance effectiveness in the treatment of depression, and in particular chronic depression. In addition, the combination of an SSRI with L-tryptophan is believed to be surprisingly effective;

this combination has the advantage of use of a low dose of L-tryptophan. The components of the medicament of this invention may be presented as a combined preparation for simultaneous, separate or sequential use in the treatment of various forms of depression. It has also been observed that a parallel or simultaneous administration of vitamin B_{12} treatment, for example orally or by injection, may enhance the therapeutic effect of this combination.

It has also been found that combinations (i) vitamin B_{12} with an inducer or a precursor of a neurotransmitter and (ii) vitamin B_{12} with an antidepressant, are effective in treatment of depression.

Accordingly, in a first aspect the present invention provides the use of any one of the following components or combinations of components:

C,

A and B,

A and C or C',

B and C or C',

A, B and C or C',

wherein

A is an antidepressant or a monoamine oxidase inhibiter,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter (other than L-tryptophan),

C' is L-tryptophan,

in the manufacture of a medicament for the treatment of at least one form of depression.

In another aspect the invention provides a method of making a medicament for the treatment of a patient suffering from depression, comprising admixing any one of the following components:

C,

A and B,

A and C or C',

B and C or C',

A, B and C or C',

wherein

A is an antidepressant or a monoamine oxidase inhibiter,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter (other than L-tryptophan),

C' is L-tryptophan,

with at least one pharmaceutically acceptable component or vehicle to prepare a medicament suitable for administration to a patient.

In yet another aspect the invention provides a method of treatment of a patient suffering from a form of depression, comprising administering to the patient any one of the following combinations of components:

I. A, B and C or C'

II. A and B

III. B and C or C'

IV. A and C or C'

wherein

A is an antidepressant or a monoamine oxidase inhibitor,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter (other than L-tryptophan),

C' is L-tryptophan,

said components being administered simultaneously or separately, in amounts which in combination have the effect of ameliorating the depressive condition.

In a further aspect the invention provides a pharmaceutical composition containing as the only pharmaceutically active components or including as the components any combination as set out above.

Treatment may be simultaneous or separate including sequential administration of the components.

In the medicaments of the invention, there may be included at least one pharmaceutically acceptable component or vehicle such as an incipient, carrier, buffer, stabiliser or other material, as discussed below.

Also provided is a kit or pack containing components A and B, or A and C or C', or A and B and C or C', or B and C or C', wherein component A the components being formulated for simultaneous, separate or sequential

delivery in the treatment of depression. Particularly components A and C or C' may be combined, and component B separate.

The depression with which the present invention is concerned may be characterised by its chronic nature as a result of the neurotransmitter disturbance.

In addition to depression, the present invention is applicable to any and all depressive illnesses associated with all psychiatric conditions and exogenous and endogenous depression.

Preferred antidepressants for use in the present invention include tricyclic and tetracyclic antidepressants such as lofepramine and selective serotonin re-uptake inhibitors (SSRI). Lofepramine and certain other tricyclic antidepressants also show some monoamine oxidase inhibitor (MAOI) activity. Other suitable antidepressants and MAOIs include mianserin, trimipramine, imipramine, clomipramine, amitriptyline, protriptyline, nortriptyline, fluvoxamine, fluoxetine, maprotiline, sertaline, venlaflaxine, pargyline, triazolopyridine, phenelzine, tranylcypromine, desipramine, moclopemide, dothiepin, doxepin, paroxetine, oxazine, viloxazine, mirtazapine and nefazadone amongst others.

Particularly of interest is the combination of a SSRI with L-phenylalanine or L-tryptophan. The case study below demonstrates effectiveness of fluoxetine in

such a combination. The same effect is expected for other SSRIs, e.g. lofepramine and paroxetine.

A neurotransmitter inducer is a component which enhances or triggers production of a neurotransmitter.

A preferred neurotransmitter precursor for use in the present invention is L-phenylalanine (LPA).

Other amino acids such as L-tyrosine or other compounds such as tyramine may also find use in the present invention as a neurotransmitter, inducer or precursor. L-tryptophan is also useful, as indicated above.

Compounds may be provided as a metabolite of a precursor. For example, L-phenylalanine may be provided as a metabolite of aspartame.

If the combination for treatment includes vitamin B_{12}, this may be in the form of cyanocobalamin or hydroxycobalamin, to be administered orally or intramuscularly.

The compositions provided herein may comprise an antidepressant, a monoamine oxidase inhibitor (MAOI) or a selective serotonin re-uptake inhibitor (SSRI) and a neurotransmitter precursor or inducer, or any other combination of components disclosed herein, as combined (simultaneous or sequential) actives. However, compounds may be employed which mimic a given active in improving diagnostic status and/or ameliorating one or more symptoms of depression (mimetics). Such compounds and

their use are within the scope of the present invention. Also within the scope of the present invention are derivatives or analogues of the antidepressant, MAOI or SSRI which retain the antidepressant, MAOI or SSRI activity, respectively.

In accordance with the present invention, the compositions provided may be administered to individuals. Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, e.g. decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors. Dose regimens for the MAOIs, SSRI and tricyclic antidepressants may be within the range used for the treatment of depression (for which the standard starting dose of lofepramine is 140mg per day). With the proviso that the prescribing physician will be able to decide suitable and safe dosage levels, a possible range for administration of antidepressants is 10-210mg per day, although 50-70mg per day may be suitable. For the neurotransmitter precursors or inducers, a range of 100mg to 5g per day, preferably 500-2000mg/d (mg per day) may be employed, the dose increasing in proportion to the level of antidepressant

or MAOI employed.

As an example, a 70mg dose of lofepramine may be combined with 500mg of L-phenylalanine given in the morning, this being supplemented with a further 500mg of L-phenylalanine given in the afternoon.

Where vitamin B_{12} is co-administered, the amounts may be those generally recommended for daily intake of the vitamin or may be greater than that recommended as average daily intake. The preferred average dosage range for vitamin B_{12} in the invention is from 1mg every 3 months up to 1mg every 3 days. When symptoms are severe, this may be 1mg intramuscular hydroxycobalamin per week in an 8-10 week course at the start of treatment, perhaps reduced to 1mg every 10 days as treatment progresses. The desired dosage level of vitamin B_{12} may conveniently be given by weekly intramuscular injection, but doses ranging from 5µg to 10mg may be given daily orally.

Pharmaceutical compositions according to the present invention, and for use in accordance with the present invention, may comprise, in addition to active ingredient, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, e.g.

cutaneous, subcutaneous or intravenous.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included.

For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required. L-tryptophan and L-phenylalanine are available in 500mg tablets.

A combined oral preparation in single tablet form, containing all these components A, B and C or C', or for example components B and C or C', is feasible. Alternatively, a treatment pack may contain the components separately.

EXAMPLES

Case #1

A 49 year old male with chronic depression who was depressed, sometimes relatively severely, for over 20 years was being treated with 30mg fluoxetine once daily, requiring increasing doses to sustain antidepressant effects. Previous treatment with prothiaden had been relatively ineffective and the patient complained of side effects. Thus a return to tricyclic antidepressants was not recommended. He was commenced on a combination of fluoxetine 30mg, L-phenylalanine 500 mg and vitamin B_{12} 2000 μg orally, all once daily, with a sudden improvement in his depressive condition. His mood had improved and indeed he was as a consequence able to re-establish a relationship with his social partner that very day. He continues to improve clinically on the combination treatment.

It will be apparent to those skilled in the art that variations and modifications to the specific embodiments disclosed herein may be made without departing from the scope of the invention.

CLAIMS

1. Use of any one of the following components or combinations of components:

C,

A and B,

A and C or C',

B and C or C',

A, B and C or C',

wherein

A is an antidepressant or a monoamine oxidase inhibiter,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter (other than L-tryptophan),

C' is L-tryptophan,

in the manufacture of a medicament for the treatment of at least one form of depression.

2. Use according to claim 1, wherein the depression is chronic (cyclothymic) depression.

3. Use according to claim 1 or 2, wherein the depression is severe depression.

4. Use according to claim 1, 2 or 3, wherein A is a tricyclic or tetracyclic antidepressant or a selective

serotonin re-uptake inhibitor (SSRI).

5. Use according to claim 4, wherein A is lofepramine, fluoxetine or paroxetine.

6. Use according to any one of claims 1 to 5, wherein B is in the form of cyanocobalamin or hydroxycobalamin.

7. Use according to any one of claims 1 to 6, wherein C is L-phenylalanine, L-tyrosine, or tyramine.

8. Use according to any one of claims 1 to 6, wherein the combination of components is L-tryptophan and a SSRI.

9. Method of making a medicament for the treatment of a patient suffering from depression, comprising admixing any one of the following components or combinations of components:

C,

A and B,

A and C or C',

B and C or C',

A, B and C or C',

wherein

A is an antidepressant or a monoamine oxidase inhibiter,

B is vitamin B_{12}, and

C is a precursor or inducer of a neurotransmitter (other than L-tryptophan),

C' is L-tryptophan,

with at least one pharmaceutically acceptable component or vehicle to prepare a medicament suitable for administration to a patient.

10. Method according to claim 9, wherein said medicament contains one of the following combinations of components:

A, B and C or C',

A and B,

B and C or C',

A and C or C',

in a form or forms suitable for simultaneous or separate administration.

11. Method according to claim 9 or 10, wherein the depression is severe depression.

12. Method according to claim 9, 10 or 11, wherein the neuropathy is chronic depression.

13. Method according to any one of claims 9 to 12, wherein A is a tricyclic or tetracyclic antidepressant or a selective serotonin re-uptake inhibitor.

14. Method according to claim 13, wherein A is lofepramine, fluoxetine or paroxetine.

15. Method according to any one of claims 9 to 14, wherein B is in the form of cyanocobalamin or hydroxycobalamin.

16. Method according to any one of claims 9 to 15, wherein C is L-phenylalanine, L-tyrosine, or tyramine.

17. Method according to any one of claims 9 to 15 wherein the combination of components is L-tryptophan and a SSRI.

18. Method of treatment of a patient suffering from a form of depression, comprising administering to the patient any one of the following combinations of components:

I. A, B and C or C'

II. A and B

III. B and C or C'

IV. A and C or C'

wherein

A is an antidepressant or a monoamine oxidase inhibitor,

B is vitamin B_{12}, and

C is a precursor or inducer of a

neurotransmitter (other than L-tryptophan),

C' is L-tryptophan,

said components being administered simultaneously or separately, in amounts which in combination have the effect of ameliorating the depression.

19. Method according to claim 18 wherein the depression is chronic depression.

20. Method according to claim 18 and 19 wherein the neuropathy is severe depression.

21. Method according to any one of claims 18 to 20, wherein A is a tricyclic or tetracyclic antidepressant or a selective serotonin re-uptake inhibitor.

22. Method according to claim 21, wherein A is lofepramine, fluoxetine or paroxetine.

23. Method according to any one of claims 18 to 23, wherein B is in the form of cyanocobalamin or hydroxycobalamin.

24. Method according to any one of claims 18 to 23, wherein C is L-phenylalanine, L-tyrosine or tyramine.

25. Method according to any one of claims 18 to 23,

wherein the combination of components is L-tryptophan and a SSRI.

26. A pharmaceutical composition for treatment of depression having a combination of pharmaceutically active components consisting only of or including any one of the combinations set out in claim 18.